Remarks

Election/Restrictions

In response to the Restriction Requirement, Applicants hereby confirm their election of Group I, claims 1-35, 46-54 and 96-105.

Sequence Listing

A sequence listing and associated documents and diskette in compliance with 37 C.F.R. §§ 1.821-1.825 are enclosed herewith.

Oath/Declaration

A new declaration in compliance with 37 C.F.R. § 1.67(a) is enclosed herewith.

Claims

Independent claims 1 and 46 have been amended as further discussed below. Claim 3 has been amended to indicate that the transgene comprises at least a portion of an intron. Support for this amendment is found at p. 57, lines 10-11 (paragraph 129). Claims 12 and 13 have been amended to include horseradish peroxidase and alkaline phosphatase among the detectable markers. Support for this amendment is found at p. 54, lines 18-19 (paragraph 123). New claim 114 is drawn to a specific embodiment of the transgenic nematode of claim 12 in which the detectable marker is alkaline phosphatase.

New independent claims 106 and 110 are drawn to methods of expressing a polynucleotide in a *C. elegans* nematode comprising the step of generating a transgenic *C. elegans* nematode, cells of which comprise a *vap-1* regulatory region (claim 106) or a *vap-2* regulatory region (claim 110) operably linked to the polynucleotide; and maintaining the nematode so that expression of the polynucleotide occurs. These claims are supported by original claims 100 and 105 and by Examples 4 (pp. 76-77) and 6 (p. 80) describing, respectively, the construction and analysis of transgenic *C. elegans* carrying vap-1::gfp and vap-1::nls-gfp reporter transgenes (Example 4) and the construction of transgenic *C. elegans* carrying vap-2::gfp and vap-2::nls-gfp reporter transgenes. Further support is provided by Example 8 (pp. 81-82), describing construction and analysis of transgenic *C. elegans* carrying a different reporter

transgene, vap1::myc. Dependent claims 107-109 and 111-113 are supported by original claims 97-99 and 102-104 and by the portions of the specification mentioned above.

New claim 115 is drawn to a method of generating a transgenic *C. elegans* nematode comprising steps of (a) selecting a parasitic nematode secretory protein that is expressed in a pharyngeal gland cell, an amphidial gland cell, or both; (b) identifying a *C. elegans* homolog of the protein selected in step (a); and (c) generating a transgenic *C. elegans* nematode, wherein cells of the transgenic nematode comprise a transgene comprising a first DNA element encoding a detectable marker operably linked to a second DNA element whose sequence comprises a sequence located up to 10 kb immediately upstream of the start codon of the gene that encodes the *C. elegans* homolog. Support for this claim is found throughout the specification and original claims, e.g., at original claim 46 and at p. 56, lines 6-9 (paragraph 126), which states that in certain embodiments of the invention the transgene of a transgenic nematode of the invention includes up to 10 kb of genomic sequence immediately upstream from the start codon of the gene of interest. Further support is found in Example 1 (pp. 71-73), which describes identification of VAP-1, which is a *C. elegans* homolog of ASP-1, a secretory protein of the parasitic nematode *A. caninum*, in Example 3 (pp. 74-76), which describes cloning of a genomic region upstream of the *vap-1* coding sequence and construction of a transgene comprising a portion encoding a detectable marker operably linked to the upstream sequence, and in Example 4 (pp. 76-77), which describes construction of transgenic *C. elegans* nematodes comprising the transgene.

New claim 116 is drawn to a transgenic *C. elegans* nematode, cells of which comprise a first DNA element encoding a detectable marker operably linked to a second DNA element whose sequence comprises a sequence located up to 10 kb immediately upstream of the start codon of a gene that encodes a *C. elegans* homolog of a parasitic nematode secretory protein, which parasitic nematode secretory protein is expressed in a pharyngeal gland cell, an amphidial gland cell, or both, of a parasitic nematode. Support for this claim is found at the same places where support is found for claim 115, since the transgenic nematode of claim 116 can be made according to the method of claim 115. Further support for dependent claims 117-122 is found at p. 56, lines 6-9 (paragraph 126), which indicates that in certain embodiments of the invention the transgene of a transgenic nematode of the invention includes up to 6, 8, or 10 kB of genomic sequence immediately upstream from the start codon of the gene of interest, at p. 57, lines 10-11 (paragraph 129), indicating that the transgene can comprise part or all of the coding sequence,

part of all of an intron, and/or part or all of a 3' untranslated region of a gene of interest, at p. 57, lines 1-4 (paragraph 129) indicating that preferred *C. elegans* transgenes comprise genomic DNA sequence upstream of coding sequences for VAP family members, and at p. 58, lines 12-26 (paragraph 131), indicating that in certain embodiments of the invention the transgene is integrated and describing methods for so doing.

New claim 124 is drawn to a method of generating a transgenic *C. elegans* nematode comprising steps of: (a) selecting a *C. elegans* secretory protein that is expressed in a pharyngeal gland cell, an amphid sheath cell, or both; and (b) generating a transgenic *C. elegans* nematode, wherein cells of the transgenic nematode comprise a trangene comprising a first DNA element encoding a detectable marker operably linked to a second DNA element whose sequence comprises a sequence located up to 10 kb immediately upstream of the start codon of the gene that encodes the *C. elegans* secretory protein. Support for this claim is found in the same places where support for claim 115 is found, and also at p. 45, lines 3-4 (paragraph 103), which indicates that any *C. elegans* secretory protein can be used in the invention, regardless of whether a homolog in a parasitic nematode species has been identified.

New claim 125 is drawn to a transgenic nematode, cells of which comprise a trangene comprising a first DNA element encoding a detectable marker operably linked to a second DNA element whose sequence comprises a sequence located up to 10 kb immediately upstream of the start codon of a gene that encodes a *C. elegans* secretory protein. Support for this claim is found at the same places where support is found for claim 124, since the transgenic nematode of claim 125 can be made according to the method of claim 124. Further support for dependent claims 126-131 is found at the same places where support for claims 117-123 is found.

New claims 131-136 depend from claim 106, support for which is described above. These claims specify particular polynucleotides, e.g., detectable markers, and optional elements of the transgene. Further support for these claims is found in original claims 1, 3, 11-13, p. 54, lines 18-19 (paragraph 123), and p. 57, lines 10-11 (paragraph 129).

New claims 137-142 depend from claim 110, support for which is described above. These claims specify particular polynucleotides, e.g., detectable markers, and optional elements of the transgene. Further support for these claims is found in original claims 1, 3, 11-13, p. 54, lines 18-19 (paragraph 123), and p. 57, lines 10-11 (paragraph 129).

Rejections under 35 U.S.C. § 112

Claims 1-35, 46-54, and 96-105 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that the claims contain subject matter that was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that the DNA sequences of all regulatory elements of genes encoding nematode secretory products or homologs thereof have not been disclosed and that there is expected to be sequence variation among species of nematode regulatory elements. The Examiner further asserts that the specification fails to describe what DNA molecules fall within the genus and that therefore conception is not achieved until reduction to practice has occurred. Applicants respectfully traverse the rejection for each of the reasons below.

Firstly, it is not necessary for Applicant to list all sequences of useful regulatory elements of genes encoding nematode secretory products in order to show possession of the invention. As the Federal Circuit has repeatedly stated, "A specification may, within the meaning of 35 U.S.C. § 112 para. 1, contain a written description of a broadly claimed invention without describing all species that the claim encompasses," *In re Robins*, 429 F.2d 452 (1970), quoted in *Amgen v. Chugai*, 927 F.2d 1200 (1991).

Secondly, Applicants submit that it is not necessary to provide sequences of nematode regulatory elements to show that Applicants were in possession of the necessary common features or attributes possessed by the genus of nematode regulatory elements in order to describe this genus sufficiently for purposes of the present claims. In the present case, the necessary common features or attributes possessed by the genus are not in fact to be found in the sequences of the regulatory elements themselves but rather in the position of the regulatory elements with respect to coding sequences for nematode secretory products within the nematode genome. The necessary common feature possessed by members of the genus is that they comprise a portion of the genomic sequence found within 10 kb upstream of the start codon of a gene that encodes a nematode secretory product or homolog thereof, which can include up to the entire 10 kb, and that they regulate expression of an operatively linked nucleic acid. This feature is described in the specification at p.56, lines 6-9 (paragraph 126). Certain nematode regulatory elements comprise regions located within 2, 4, 6, 8, or 10 kB upstream of the start codon of a

gene that encodes a nematode secretory product or homolog thereof. However, the claims do not require narrowing down the regulatory element to a minimal region. The claims merely require that the transgene *comprises* the regulatory element. Despite the existence of sequence diversity among nematode regulatory elements, the relevant feature of such elements for purposes of describing the claimed invention, is that they comprise a portion of the genomic sequence found within 10 kb upstream of the start codon.

Providing a DNA sequence is not the only way in which the written description requirement can be met, as acknowledged in the USPTO Written Description Guidelines, 66 Fed. Reg., 1099 and confirmed in *Enzo Biochem Inc. v. Gen-Probe, Inc., et al.*, 323 F.3d 956 (Fed. Cir. 2002). In that case, Enzo had claimed particular *unsequenced* bacterial DNA inserts within plasmids that it had deposited. The Federal Circuit held that a reference in the specification to the deposits described the sequences sufficiently to the public for purposes of meeting the written description requirement since a person of ordinary skill in the art, reading the accession numbers in the specification, could obtain the claimed sequences by requesting the deposits from the ATCC and excising the sequences. Enzo also claimed subsequences of the deposited sequences and mutated versions of the sequences, with the proviso that they hybridize to the deposited sequences. Such claims could include thousands of sequences, none of which were provided, but the court held that such broad claims could still satisfy the written description requirement based on the deposits of only 3 members of the genus, none of which were sequenced. The Examiner has stated that, "One cannot describe what one has not conceived", and that, "The skilled artisan cannot envision the detailed chemical structure of the encompassed regulatory elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." It is clear, after the decision in *Enzo, Inc. v. Gen-Probe, Inc.*, that the requirement of a reduction to practice, in the sense of providing the sequence of a claimed nucleic acid, cannot be an accurate statement of the law with respect to written description.

In regard to specific claims directed to hybridizing sequences found in other bacteria, the court stated that, "as those bacteria were deposited, their bacterial genome is accessible...and they are adequately described by their accession numbers.", even though the specification did not indicate where in the bacterial genome the hybridizing sequences could be found. Thus the court clearly established that reference to accession numbers of species that contain a claimed nucleic

acid sequence, provided that the accession numbers give the public access to the invention, may be sufficient to satisfy the written description requirement even in cases where not a single sequence is actually provided and where there is not even any guidance as to the position of the claimed sequences within an entire unsequenced genome.

In the present case, Applicants have provided an extensive list of nematode orders and families (pp. 30-31. These nematodes are known in the art and are readily obtainable from a variety of laboratories that study them, from the Carolina Biological Supply Co., Burlington, NC, or by isolating them from nature or from domestic animals using known methods. The strains are therefore available to the public as a source of genetic material for isolation of DNA that lies up to 10 kb upstream of the start codon of a gene that encodes a nematode secretory protein, just as the bacterial species in *Fiddes* were available. Applicants have further provided accession numbers for numerous nematode secretory proteins (see, e.g., Table 1 on p. 23). Additional *C. elegans* genes are referenced based on their location within numbered cosmids (see, e.g., p. 74, lines 6-13 (paragraph 170), mentioning 11 VA family members and providing their cosmid location, and p. 57, lines 7-8 (paragraph 129), mentioning additional *C. elegans* genes and providing cosmid locations for some of these. Cosmid locations for the others could readily be obtained by one of ordinary skill in the art by searching the *C. elegans* genome sequence, which was publicly available as of the filing date of the application (as mentioned at p. 38, line 31 – p. 39, line 8), and allows the positioning of any *C. elegans* sequence with respect to a set of overlapping cosmids covering the entire *C. elegans* genome. These cosmids were available upon request from the Sanger Center in Cambridge, England, as of the filing date of the application. This information, taken together with the description that the nematode regulatory elements comprise a region up to 10 kb of sequence upstream of the start codon of a gene that encodes a nematode secretory protein, is sufficient to describe the claimed invention. In the instant case, one of ordinary skill in the art could readily obtain the sequences, analogous to the situation in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*

Third, even if it were necessary to provide DNA sequences of the regions 5' to coding sequences of nematode secretory products or homologs thereof to meet the written description requirement, Applicants submit that this requirement is met since the entire *C. elegans* genome was sequenced and made publicly available as of the filing date of the application. The physical position of every *C. elegans* coding sequence, including those of the numerous *C. elegans*

secretory products or homologs thereof mentioned in the specification was known. Thus the sequences up to 10 kb in length and located immediately 5' to these coding regions were likewise known to one of ordinary skill in the art. Furthermore, sequence information for nematode secretory proteins from a variety of other nematode species, including various parasitic nematode species, was also available in the public domain as of the filing date of the application

Fourth, the Examiner has indicated that "Possession may be shown by an actual reduction to practice..." Applicants have described such a reduction to practice. Examples 4-9 (pp. 76-84) describe construction of a variety of different transgenic *C. elegans* nematodes, cells of which contain a transgene comprising a regulatory element of a gene that encodes a nematode secretory product or a homolog thereof operably linked to a DNA sequence encoding a detectable marker. The nematodes contained regulatory elements of either *vap-1* or *vap-2*, both of which are nematode secretory proteins or homologs thereof.

Finally, Applicants submit that the situation with respect to the instant claims is readily distinguishable from that in the cases cited by the Examiner, such that it is inappropriate to mechanically and loosely apply the holdings of those cases to reject the instant claims. The major concern in those cases, and the reason for holding various claims lacking in written description, was that the applicants described *particular claimed DNA sequences* solely in terms of their function. The present claims are not drawn to specific sequences of the genus of regulatory elements of nematode secretory products or homologs thereof or even to a single such sequence. Indeed Applicants could not claim this genus since the sequences of many members are known in the art. Instead, the claims are directed to a genus of transgenic nematodes comprising a transgene that incorporates members of the genus of regulatory elements, which are described by reference to their position with respect to coding sequences for nematode secretory proteins, and to methods of making or using the transgenic nematode, a context which is quite different to that in the cases cited by the Examiner.

For example, as stated by the Examiner, in *Fiddes v. Baird*, claims directed to mammalian FGFs were held unpatentable. The claims in question required "an isolated or synthetic, substantially pure DNA sequence encoding mammalian FGF". The specification provided a single sequence, which encoded bovine FGF. Unlike the situation in *Fiddes v. Baird*, Applicants are not claiming particular DNA sequences that encode specific proteins. Furthermore, Applicants are not attempting to claim an entire genus based on only one species.

Instead, Applicants have listed a large number of nematode secretory proteins, regulatory elements of which could be used in claim 1. For example, Applicants identified numerous members of the VAP protein family in *C. elegans* (see Example 2, pp. 73-74) and described other nematode secretory proteins as mentioned above.

In *Lilly*, Applicants were also attempting to claim particular DNA sequences that encoded specific insulin proteins, unlike the case here. In *Lilly*, the court complained that a definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568 (1997). Here, in contrast, Applicants have described what the nematode regulatory element is in structural terms, i.e., it comprises a fragment of DNA having a length of up to 10 kb located immediately 5' to a coding sequence for a nematode secretory protein or homolog thereof. Applicants have provided numerous examples of nematode secretory proteins or homologs thereof that are known in the art and have also described various common attributes thereof (e.g., possession of a signal sequence, expression within known nematode secretory organs, presence of the product within nematode secretions). Applicants have demonstrated a reduction to practice for members of the claimed genus. For each of the reasons above, Applicants respectfully request withdrawal of the rejection.

Claims 1-35, 46-54, and 96-105 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. The Examiner has asserted that the claims are lacking in enablement as to transgenic nematodes other than *C. elegans*. As discussed above, all of the claims have been amended to encompass only transgenic *C. elegans* nematodes and methods for making and using them.

The Examiner has further asserted that, "the specification fails to provide any relevant teachings or specific guidance with regard to the nematode regulatory elements embraced by the claims". Applicants respectfully disagree. As described above, Applicants teach that the regulatory elements comprise a portion of the genomic sequence found within 10 kb upstream of the start codon of a gene that encodes a nematode secretory product or homolog thereof. This feature is described in the specification at p.56, lines 6-9 (paragraph 126). Certain nematode regulatory elements comprise regions located within 2, 4, 6, 8, or 10 kB upstream of the start

codon of a gene that encodes a nematode secretory product or homolog thereof. However, the claims do not require narrowing down the regulatory element to a minimal region. The claims merely require that the transgene *comprises* the regulatory element. In order to practice the invention the skilled artisan may use up to the entire 10 kb, which will encompass a regulatory element, or may use smaller portions if desired. As described above, DNA sequences upstream of numerous genes encoding nematode secretory proteins or homologs thereof were known in the art as of the filing date of the application, and additional nucleic acids could readily be obtained. Applicants have demonstrated a reduction to practice of the invention with respect to regulatory elements upstream of the coding sequence in the *vap-1* and *vap-2* genes. In the particular reduction to practice described in the specification, portions of between 4 and 5 kB of genomic sequence were used. However, longer or shorter portions could also have been employed if convenient. Furthermore, knowledge of the sequence is not needed to practice the claims.

The Examiner has also stated that, "the specification has failed to provide any guidance, working examples, or relevant teachings that would allow the skilled artisan to use any nematode regulatory elements when practicing the claimed invention". Applicants respectfully disagree. As mentioned above, Applicants have provided working examples involving construction of transgenic nematodes cells of which contain reporter constructs that include regulatory elements found upstream of either the *vap-1* or *vap-2* coding sequences. Isolation of these upstream sequences, construction of the reporter constructs, and creation of the transgenic *C. elegans* utilized standard molecular biology and is fully described in the specification. The methods could readily be applied to regulatory elements of genes that encode other nematode secretory proteins or homologs thereof.

The Examiner has stated that "Regulatory elements such as promoters have specific 5' and 3' boundaries as well as particular transcription factor binding elements." Applicants point out that the Examiner has not provided any evidence in support of the statement that promoters have specific 5' and 3' boundaries. While it is clear that removal of certain sequences at either the 5' or 3' end of promoter regions can abrogate their function and that certain sequences lying outside promoter regions are not necessary for promoter activity, Applicants are not aware of a method that can unambiguously determine specific 5' and/or 3' boundaries of promoters. Even if it were possible to unambiguously determine specific 5' and/or 3' boundaries of promoters, it

is not necessary to do in order to enable the instant claims. The claims merely require use of a DNA sequence that comprises a regulatory element and do not require exclusion of adjacent sequences that may not be necessary for activity of the regulatory element.

The Examiner has also stated that, "the art suggests that promoters from particular species of nematodes do (sic) function equivalently in other species of nematodes" and mentions an example in which promoters from parasitic nematodes, when introduced into *C. elegans*, result in spatial expression correlating to expression profiles in the parasite but that the timing of expression failed to correlate. The Examiner states that the timing of expression could affect any resulting phenotype. However, the claims do not require that the timing of expression is identical or that any resulting phenotype is identical. Furthermore, the regulatory elements in the claimed transgenic nematodes direct expression of genes encoding detectable markers, which would not be expected to produce any physiologically relevant phenotype other than production of a detectable marker. The example cited by the Examiner actually supports enablement of the instant claims since it describes introduction of a regulatory element from a parasitic nematode into *C. elegans* and shows that expression occurred in corresponding spatial locations.

The Examiner makes several additional assertions but does not point out their relevance with respect to enablement of the instant claims, saying only that, "the state of the art sets forth a level of unpredictability". For example, the fact that expression levels of heterologous proteins may vary according to target cell or promoter does not mean that the instant claims lack enablement as the claims do not require particular expression levels and do not require that such levels may not vary. The fact that different levels of expression of human α-synuclein occurred in *C. elegans* when the gene was under the control of different promoters is to be expected and does not suggest unpredictability. In any event, it has no relevance for the instant claims. The fact that certain proteins from one nematode species may not result in rescue when introduced into nematodes of other species that contain loss-of-function mutations in similar genes is also not relevant as the instant claims do not involve expressing proteins from a first nematode species in a second nematode species in order to rescue a loss-of-function mutation. The specification, the example cited by the Examiner, and many other examples in the scientific literature show that such detectable markers are readily expressed in *C. elegans* when placed under control of a variety of regulatory elements.

For each of the above reasons Applicants submit that the instant claims are fully enabled and respectfully request withdrawal of the rejection.

Claims 96-105 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 96-105 have been canceled. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1-2, 5-6, 10-12, 14-29, 46, 48-50, and 53-54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Plenefisch, et al., *Mol. Biochem. Parasitol.*, 105:223-236 (2000), hereinafter "Plenefisch". Original claim 1 was drawn to a transgenic *C. elegans* nematode, the cells of which contain a transgene comprising a regulatory element of a gene that encodes a nematode secretory product or a homolog thereof operably linked to a DNA sequence encoding a detectable marker. The claim has been amended to recite particular embodiments of the invention in which the detectable marker is expressed in a *C. elegans* pharyngeal gland cell or amphid sheath cell. Support for the amendment is found in original claim 26, which requires that the detectable marker is expressed in a dorsal pharyngeal gland, original claim 28, which requires that the detectable marker is expressed in the subventral pharyngeal gland, and original claim 30, which requires that the detectable marker is expressed in an amphid sheath cell.

Plenefisch teaches trangenic *C. elegans* whose cells contain a transgene comprising a promoter of any of various genes that are *C. elegans* homologs of an *Ascaris suum* gene encoding a secreted protein operably linked to a DNA sequence encoding a detectable marker. The *C. elegans* genes are *lbp-1*, *lbp-2*, and *lbp-3*. The Examiner asserts that the expression patterns of the secreted LBP proteins suggest that they may be expressed and secreted through the pharyngeal glands and refers to pp. 230-232 in support of this assertion. Applicants respectfully disagree. On p. 230, with respect to *lbp-1*, Plenefisch states that, "Expression of GFP was first detected in a group of eight to ten unidentified cells at about the time of gastrulation...The location of these cells is consistent with their identification as hypodermal precursors...From the two-fold state through threefold stages of *C. elegans*, expression was localized exclusively to hyp-7 nuclei...the expression of GFP from L1 to adult stages could be detected in a single unidentified neuron in the ventral cord." On pp. 230-231, Plenefisch states

with respect to constructs containing the *lbp-2* promoter that, "GFP expression was not observed in the hypodermis but instead appeared to be restricted to body wall muscle...Only body wall muscles abutting the pseudocoelom showed expression, suggesting that the LBP-2 protein may be secreted into the perienteric fluid of the pseudocoelom." On p. 231, with respect to constructs containing the *lbp-3* promoter, Plenefisch states that, "GFP was expressed in presumptive hypodermal cells by the comma state and in posterior body wall muslce cells by the two fold stage. From L1 to adult stages, GFP continued to be expressed in body wall muscle cells adjacent to the pseudocoelom." Thus in contrast to the Examiner's assertion, the expression patterns do not suggest that LBP proteins are expressed or secreted through the pharyngeal glands. Instead, the proteins are expressed in hypodermal cells, muscle cells, or one of the many *C. elegans* neuronal cells. Furthermore, Plenefisch explicitly states on p. 224 in the first full paragraph of the right column that, "the expression patterns of *lbp-1*, *lbp-2*, and *lbp-3*, examined with GFP reporter constructs, are consistent with secretion into perivitelline and perienteric fluids from *hypodermis* and *muscle* respectively" (italics added). Pharyngeal gland cells are distinct from hypodermis and muscle tissue. Thus the detectable marker is not expressed in either a pharyngeal gland or amphid sheath cell as required by amended claim 1.

Original claim 46 was drawn to a method of generating a nematode comprising steps of (a) selecting a parasitic nematode secretory protein; (b) identifying a *C. elegans* homolog of the protein selected in step (a); (c) identifying a nucleic acid sequence comprising a regulatory region of a *C. elegans* gene encoding the *C. elegans* homolog identified in step (b); and (d) generating a transgenic nematode, wherein cells of the transgenic nematode comprise a nucleic acid sequence including the identified regulatory region operably linked to a nucleic acid sequence encoding a detectable marker. The claim has been amended to recite a particular embodiment of the invention in which the detectable marker is expressed in a pharyngeal gland cell or amphid sheath cell. Support for the amendment is found in original claim 54.

While Plenefisch does teach selecting a parasitic nematode secretory protein, identifying a *C. elegans* homolog thereof, identifying a nucleic acid sequence comprising a regulatory region of a *C. elegans* gene encoding the *C. elegans* homolog and generating a transgenic nematode whose cells comprise a nucleic acid sequence including the identified regulatory region operably linked to a nucleic acid sequence encoding a detectable marker, as discussed

above there is no evidence to suggest that the detectable marker is expressed in a pharyngeal gland cell or amphid sheath cell as required by amended claim 46.

Claims 1-2, 5-7, 10-12, 14, 19, and 25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Britton, et al., *Mol. Biochem. Parasitol.*, 103:171-181 (1999), hereinafter "Britton". Britton teaches transgenic nematodes whose cells contain a promoter of either the *H. contortus pep-1* gene or the gene encoding AC-2, operably linked to a detectable marker. Britton examines the expression pattern of the detectable marker and finds that it is expressed exclusively in gut cells in both cases (see Abstract). Thus the detectable marker is not expressed in either a pharyngeal gland cell or amphid sheath cell, as required by amended claim 1.

Claims 1-2, 4-7, 10-18, 22, 24-25, 30-31, 46, 48-50, and 52-54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Miller, DM, et al., *Biotechniques*, 26:914-921 (1999), hereinafter "Miller". Miller teaches trangenic *C. elegans* whose cells contain a transgene comprising an *unc-4*, *unc-54*, or *del-1* regulatory element operably linked to a gene encoding any of several detectable markers. The Examiner maintains that the transgenic nematodes of Miller are identical or substantially identical to those of the instant claims. While the Examiner's assertion that the *unc-4*, *unc-54*, and *del-1* genes are homologs of parasitic nematode genes may well be correct, there is no evidence to suggest that any of these genes encodes a nematode secretory product as required by claim 1. The *unc-4* gene encodes a homeodomain protein. See Exhibit A, p. 1028, Riddle, D.L., et al. (eds.), *C. elegans II*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 1997, from Appendix 1, which lists *C. elegans* genes along with brief descriptions of their features and relevant references to the scientific literature. As is well known in the art, the homeodomain is a DNA binding domain characteristic of a family of transcription factors, which are not secretory proteins but instead remain within cells. Thus *unc-4* is not a nematode secretory product or homolog thereof. The *unc-54* gene encodes a major body wall muscle myosin heavy chain. See Exhibit A, pp. 1035-1036. Thus *unc-54* is not a nematode secretory product or homolog thereof, but remains within muscle cells. The *del-1* gene is a member of the degenerin protein family, which encode a variety of membrane-bound channel proteins. See Exhibit B, which is an abstract of Tavernarakis N, et al., *Neuron*,18(1):107-19, 1997. The protein encoded by *del-1* is thus not a nematode secretory product or homolog thereof. Since the proteins encoded by *unc-4*, *unc-54*, and *del-1* are not nematode secretory products or homologs thereof, the transgenic nematodes of Miller that were generated using

constructs comprising regulatory elements of these genes do not contain a transgene comprising a regulatory element of a gene that encodes a nematode secretory product or a homolog thereof, as required by claim 1.

Furthermore, Miller states (p. 921) that the *unc-54* promoter drives expression in body-wall and vulval muscles. It is thus evident that the constructs that include an *unc-54* regulatory element do not direct expression of the detectable marker in a pharyngeal gland cell or amphid sheath cell as required by claim 1. Miller also states (p. 921) that the *unc-4* promoter drives expression in VA motor neurons and the *del-1* promoter drives expression in VB motor neurons. The Examiner states that amphid sheath cells comprise neurons. However, this statement is incorrect. As indicated in the specification at paragraph 54 (p. lines, of the specification as filed), amphid sheath cells are supporting cells that are present within *C. elegans* amphids, where they serve to support neuronal cells. See also Exhibit A, pages 722 and 745 from Riddle, D.L., et al. (eds.)., *C. elegans II*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 1997, which describes the amphid organs and indicates that they contain both neurons and amphid sheath cells. The latter are not sensory cells but function to support or form channels for the neurons or portions thereof. Since neurons and amphid sheath cells are distinct cell types there is no evidence to suggest that the constructs disclosed in Miller would direct expression in amphid sheath cells. Indeed given that Miller specifically indicates the cell types in which expression was detected, Applicants submit that if the constructs indeed did direct expression in amphid sheath cells, it is likely that Miller would have so stated. Thus the detectable marker in the transgenic nematodes taught by Miller are not expressed in a pharyngeal gland cell or amphid sheath cell as required by claim 1.

With respect to independent claim 46, Miller does not teach selecting a parasitic nematode secretory protein at all and does not teach identifying a *C. elegans* homolog of such a protein, both of which are required by claim 46. Miller says nothing about parasitic nematodes and his teachings contain nothing about secretory proteins, as indicated above.

Claims 1, 5, 6, 7, 10-12, 14, 15-18, 24-25, 30-31, 46, 48, and 53-54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Signor, D., et al., *Molecular Biology of the Cell*, 10:345-360 (1999), hereinafter "Signor". Signor teaches transgenic *C. elegans* expressing a detectable marker whose expression is driven by a promoter from the gene that encodes Osm-3, a *C. elegans* kinesin family member. The Examiner maintains that the transgenic nematodes of

Signor are identical or substantially identical to those of the instant claims. While the Examiner's assertion that the *C. elegans* gene that encodes Osm-3 is a homolog of a parasitic nematode gene may well be correct, there is no evidence to suggest that this gene encodes a nematode secretory product as required by the claim 1. As Signor indicates on p. 346, kinesins are motor proteins that drive *intracellular transport*. As such, these proteins would be expected to remain within cells rather than be secreted. Therefore, the transgenic nematodes of Signor that were generated using constructs comprising the *osm-3* promoter do not contain a transgene comprising a regulatory element of a gene that encodes a nematode secretory product or a homolog thereof, as required by claim 1.

Furthermore, Signor teaches that Osm-3 is expressed in amphid, inner labial, and phasmid chemosensory neurons. The Examiner states that, "The OSM-3 promoter directs expression of the green fluorescent protein in the neurons of the amphid sheath..." Applicants question what is meant by "a neuron of the amphid sheath". As pointed out above, the sensory organs known as amphids contain both neurons and amphid sheath cells, which are distinct from neurons. Signor teaches expression of GFP in neurons, and there is no evidence to suggest that the Osm-3 promoter would drive expression in amphid sheath cells. Given that Signor specifically indicates the cell types in which expression was detected, Applicants submit that if the constructs indeed did direct expression in amphid sheath cells, it is likely that Signor would have so stated. Thus the constructs of Signor do not drive expression of a detectable marker in a pharyngeal gland cell or amphid sheath cell, as required by claim 1.

With respect to independent claim 46, Signor does not teach selecting a parasitic nematode secretory protein and thus does not teach identifying a *C. elegans* homolog of such a protein, both of which are required by claim 46. Signor says nothing about parasitic nematodes and his teachings contain nothing about secretory proteins, as indicated above.

In summary, neither Plenefisch, Britton, Miller, or Signor teaches a transgenic nematode, cells of which contain a transgene comprising a regulatory element of a gene that encodes a nematode secretory product or a homolog thereof operably linked to a DNA sequence encoding a detectable marker, wherein the detectable marker is expressed in a pharyngeal gland cell or amphid sheath cell as required by claim 1 as amended. Withdrawal of the rejection of claim 1 and claims dependent on claim 1 for anticipation is respectfully requested. In addition, neither Plenefisch, Miller, or Signor teaches a method of method of generating a nematode that includes

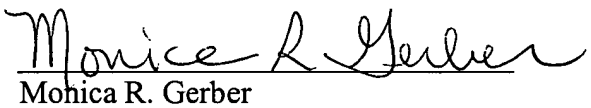
steps of selecting a parasitic nematode secretory protein, identifying a *C. elegans* homolog of the protein, identifying a nucleic acid sequence comprising a regulatory region of a *C. elegans* gene encoding the *C. elegans* homolog, and generating a transgenic nematode, wherein cells of the transgenic nematode comprise a nucleic acid sequence including the identified regulatory region operably linked to a nucleic acid sequence encoding a detectable marker that is expressed in a pharyngeal gland cell or amphid sheath cell as required by amended claim 46. Withdrawal of the rejections of claim 46 and claims dependent on claim 46 is respectfully requested.

In conclusion, in view of the amendments and remarks presented herein, the application and pending claims comply with the requirements of 35 U.S.C. §102. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful in resolving any remaining issues, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

A check to cover the fee for a one month extension of time is enclosed. Please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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3728174_1.DOC

EXHIBIT A

C. ELEGANS II

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IV. CELLULAR ANALYSIS OF CHEMOSENSORY AND THERMOSENSORY NEURONS

Three types of sensory organs in *C. elegans* hermaphrodites appear to be chemosensory, based on the fact that they are associated with openings in the cuticle that allow the enclosed neurons to contact the outside world (Fig. 2, top) (Ward et al. 1975; Ware et al. 1975). Two bilaterally symmetric amphids in the animal's head each contains the endings of 12 types of sensory neurons, two bilaterally symmetric phasmids in the tail each contains the endings of two types of sensory neurons, and six inner labial sensory organs in the head each contains the endings of two types of sensory neurons. Amphid neurons responsible for chemosensory and thermosensory behaviors have been identified through behavioral analysis of animals in which defined neurons were killed using a laser microbeam. At this point, cell ablations have not revealed functions for the phasmid and inner labial sensory organs.

The 12 neurons in each amphid can be distinguished from one another by their morphology and by their connections to other neurons (Fig. 2, bottom). Each neuron is bipolar, with one sensory process (dendrite) and one presynaptic process (axon) emanating from the cell body. The dendrites extend to the nose and terminate in sensory cilia about 5 μm long. All of the axons extend to the nerve ring, where they make synaptic connections with other neurons and each other (White et al. 1986).

The sensory neurons of the amphid can be divided into three classes based on their dendritic morphology and function (Ward et al. 1975; Ware et al. 1975). Eight types of neurons (ADF, ADL, ASE, ASG, ASH, ASI, ASJ, ASK) have one or two long slender cilia that are directly exposed to the environment through the amphid pore ("exposed" cells). These neurons detect mostly water-soluble chemicals (Table 2) (Bargmann et al. 1990; Bargmann and Horvitz 1991a,b; Kaplan and Horvitz 1993; Troemel et al. 1995). Three types of neurons (AWA, AWB, AWC) have flattened, branched cilia that are near the amphid pore, but enclosed by a support cell called the amphid sheath cell ("wing" cells). These neurons detect volatile odorants (Bargmann et al. 1993; B. Kimmel and C. Bargmann, unpubl.). One type of neuron (AFD) has a complex, brush-like dendritic membrane structure at the sensory ending which is embedded in the amphid sheath cell ("finger" cell). This neuron detects thermal cues (Mori and Ohshima 1995).

The functions of the chemosensory and thermosensory neurons inferred from cell-killing experiments are listed in Table 2. These sensory neurons are not required for postembryonic viability, but some of the amphid neurons have an essential function in regulating the dauer/non-

Russell 1975; Popham and Webster 1978; Cox et al. 1981b). The dauer cuticle has lateral ridges (alae) not present on L2, L3, or L4 larvae that are visible with Nomarski optics. A detergent-soluble 37-kD hydrophobic protein exposed on the surface of the dauer larva is not found on other stages (Blaxter 1993a). Many tissues and organs exhibit dauer-specific morphology: Pharyngeal pumping is suppressed (Cassada and Russell 1975) and the isthmus and terminal bulb of the pharynx are constricted (Vowels and Thomas 1992); the lumen of the intestine is shrunken and the microvilli are condensed (Popham and Webster 1979); the excretory gland lacks secretory granules (Nelson et al. 1983); and several sensory neurons exhibit altered position or dendrite orientation (Albert and Riddle 1983).

The anterior sensory ultrastructure of the dauer larva was examined in several specimens and compared with that of the L2 larva (Albert and Riddle 1983). In some instances, comparisons were made with L3, postdauer L4, and adult stages. Whereas sensory morphology in different nondauer stages remains constant, it differs in the dauer larva, providing an example of developmental plasticity in the nervous system (Jorgensen and Rankin, this volume). Dauer-specific sensory modifications in the amphids, inner labial neurons, and the deirids may play a part in dauer-specific behavior.

The amphids are a pair of prominent chemosensory organs located on either side of the head. Each amphid consists of two support cells and 12 neurons, eight of which are exposed to the environment through a pore in the cuticle near the tip of the head (Ward et al. 1975; Ware et al. 1975; Bargmann and Mori, this volume). Dendritic processes extend anteriorly from cell bodies located near the circumpharyngeal nerve ring, and axons extend into the ring. A sheath cell forms the channel for the dendritic processes and presumably secretes the matrix of material observed in the channel. A socket cell joins the anterior end of the channel to the cuticle. Amphidial neurons AWC, AFD, ASG, and ASI and the amphidial sheath cell are altered in shape or position in the dauer stage (Albert and Riddle 1983). Neurons ASG and ASI are displaced posteriorly within the dauer amphidial channel. Neuron AFD has significantly more microvillar projections in the dauer stage than in L2, L3, or postdauer L4 larvae. Wing-like processes of the two dauer AWC neurons form a much wider arc in transverse section, including extensive overlap of these cells. Such overlap does not occur in an L2. Whereas L2 larvae possess two separate bilateral amphidial sheath cells, the left and right sheath cells can be continuous in the dauer larva. The AWC neurons are involved in chemotaxis to volatile attractants, the AFD neurons are involved in thermotaxis, and

(dominant and semidominant): *n496, n775* (strongly dominant), *n494* (weakly semidominant), etc. Complex complementation among *unc-1* alleles. [Park and Horvitz 1986a; Morgan and Sedensky 1994] [CW]

unc-2 X –13.67 e55 : weak kinker, sluggish, thin; hypersensitive to serotonin, fails to desensitize to dopamine. ES3 ME2. OA>10: *e97, e129, e2379* (Unc, only subtle defect in adaptation), *mu74* (resembles *e55*, deletion, probable null), *pk95*tci, etc.

CLONED: 7.5-kb transcript, present throughout development, encodes protein homologous (41–65%) to α1 subunit of mammalian neuronal voltage-sensitive calcium channel.

[Schafer and Kenyon 1995] [DM]

unc-3 X 18.54 e151 : weak coiler tends to coil, tail active, good head movement; very disorganized ventral nerve cord; mosaic analysis indicates mutant focus in ventral cord motor neurons; similar phenotype in *e151/Df*. ES3 ME1. OA>5: *e54* (weaker allele), *e95, mn419, p1001*, etc.

CLONED: polymorphisms identified in *mn419* and derivatives (cosmid F42D1).

[Brenner 1974; Herman 1987] [NG, SP]

unc-4 II 1.72 e120 : large, healthy, active, moves forward well but cannot back; ventral cord VA motor neurons have normal anatomy but most have synaptic inputs appropriate to VB motor neurons. ES3 ME1. OA>15: *e26, e2151, e2308, e2320* (deletion null, resembles *e120*), *e2322*ts (TSP L2-L3), *wd1*, etc. See also *unc-37*.

CLONED: rare 1.2-kb transcript, encodes homeoprotein (pka *ceh-4*); *unc-4:lacZ* expressed in VA but not VB motor neurons.

[White et al. 1992; Miller et al. 1992] [NC]

unc-5 IV 1.96 e53 : severe coiler, grows well; L1 also severe coiler; dorsal hypodermal cells abnormal, dorsal nerve cord absent or almost absent, cord commissures fail to reach targets; muscle arms misdirected; distribution of cell bodies in ventral cord disorganized; abnormal gonad arms; Egl-c. ES3 ME0. OA>10: *e553* (resembles *e53*), *e152* (weaker phenotype behaviorally and anatomically, dorsal cord partially formed), *bx8, ev447, st1001*tci, etc. See also *unc-6, unc-40*.

CLONED: 3.0- and 3.1-kb transcripts (different 5′), encode predicted 919-aa transmembrane protein, two Ig domains and two TSP domains; mosaic analysis indicates autonomous action in neurons, DTC; ectopic expression in touch cells can cause improper dorsalward migration.

[Hedgecock et al. 1990; Leung-Hagesteijn et al. 1992; Hamelin et al. 1993] [NW]

unc-6 X –2.17 e78 : slight kinker, poor backing; large, healthy, slightly fat; dorsal extensions of DD and VD neurons grow in aberrant directions, fail to reach dorsal cord; ventral cord disorganized; abnormal gonad arms, etc. ES3 ME1. OA>20: *e7, e181, ev400* (pka *unc-106*, uncoordinated, high frequency of phasmid axon displacement), *n593, n594*, etc. Some alleles (*rh202, rh204, rh402*, etc.) defective only in dorsalward migrations; null alleles defective in both dorsalward and ventralward migrations; see also *unc-5, unc-40*.

CLONED: encodes extracellular matrix component (591 aa plus 21-aa signal

CLONED: encodes predicted 301-aa novel protein, possible transmembrane domain.

[Lewis et al. 1980] [MT, WS, ZZ]

unc-51 V 24.42 e369 : amb; paralyzed dumpy tends to curl; Egl; dorsal extensions of DD and VD neurons grow in aberrant directions, fail to reach dorsal nerve cord; amphid, phasmid, PDE, and other axons abnormal; multiple defects in axon elongation, fasciculation, etc. Abnormal axon ultrastructure: varicosities, cisternae, abnormal vesicles. ES3 ME0. OA>10: *e389, e432, e584, e1212*, etc.

CLONED: 3.1-kb transcript, encodes predicted 856-aa protein with similarity to Ser/Thr kinases; *unc-51:lacZ* expressed in neurons.

[Hedgecock et al. 1985; McIntire et al. 1992; Ogura et al. 1994] [FK, FR]

unc-52 II 23.33 e444 : adults limp, paralyzed except for head region; thin; Egl; larvae move well; progressive dystrophy, body muscles fail to accumulate myofilaments; class-1 allele. ES3 (adult) ME0. OA>10 (class 1): *e669*amb (well suppressed), *e998* (stronger phenotype), *su200, r290*, etc. Also class-2 mutations: *st549* (lethal, severe Pat, no organized myofilament lattice; probable null), *st546, st560*, etc. (all similar to *st549*). Also class-3 mutation: *ut111* (lethal, arrest at 2-fold; not paralyzed; complements class-1 alleles). See also *sup-38, smu.*

CLONED: multiple transcripts (4.0, 6.5, 8.0 kb) generated by alternative RNA processing; encode proteins related to perlecan (matrix heparan sulfate proteoglycan).

[Rogalski et al. 1993, 1995] [DM]

unc-53 II 3.07 e404 : sluggish, poor backing, dumpyish; somewhat Egl; multiple defects in neuronal outgrowth, branching; also defects in excretory canal extension, gonad arm growth; males have abnormal bursal anatomy. ES2 ME0. OA>5: *n152, n166, n569* (synergizes with *sem-5[n177]* to give strong Sem migration defect), *e2432, e2499*, etc. Null phenotype uncertain; some lethality in strong alleles.

CLONED: multiple transcripts (different 5′ends); one encodes 1528-aa protein, predicted to bind actin, ATP/GTP; may interact with SEM-5; transgene overexpression leads to extension of growth cones along A-P axis.

[Hedgecock et al. 1987; Hekimi and Kershaw 1993] [UG]

unc-54 I 27.21 e190 : limp paralyzed phenotype at all stages; larvae can move slightly more than adults; Egl; muscle ultrastructure very disorganized, few thick filaments. ES3 ME0. OA>50 (recessive): *e1108*amb, *e1301*ts, *e675*sd, and *s291* (in-frame internal deletion mutants, almost paralyzed, slight twitchers), etc. Also unusual suppressor alleles, OA>15: *s74* (dominant suppressor of *unc-22[s12]*, recessive slow, stiff; normal muscle ultrastructure). Also dominant antimorphic alleles, OA>10: *e1152*sd (severe rigid paralysis, small; *e1152*/+ paralyzed weaker phenotype. ES3 ME0), *r344* (recessive lethal, *r344*/+ severely paralyzed), etc. Intragenic revertants have recessive paralyzed phenotype; some recessive alleles (*r274, e1420*, etc.) are dominant antimorphs in *smg* background.

CLONED: encodes MHC B (MYO-4), major body wall muscle myosin heavy chain; 6-kb message, 1117-aa protein; extensive molecular analy-

sis.

[Epstein et al. 1974; McLachlan and Karn 1982; Dibb et al. 1989; Bejsovec and Anderson 1990] [TR, RW]

unc-55 I 2.36 e402 : slow, very poor backing, tends to coil ventrally; healthy; abnormal VD neurons (adopt DD synaptic pattern); mosaic analysis indicates focus in VD neurons. ES3 ME0. OA>11: *e523*, etc. [Walthall and Plunkett 1995] [ER]

unc-56 = *unc-29*

unc-57 I –0.99 e406 : strong kinker, active; small and thin; slow pharyngeal pumping; tends to hypercontract. ES3 ME2. OA>5: *e590, e957, e1190, st199, ad592*, etc. [Brenner 1974; Avery 1993a] [DA]

unc-58 X 1.51 e665 : dm; "shaker," animals short, rigidly paralyzed with constant shaking of body; *e665*/+ phenotype similar but weaker, animals slightly longer and less rigid; muscle hyperactivated, sticky pumping, short. ES3 ME0. OA4 (dominant): *e415, n495* (similar), *e778* (weaker phenotype), etc. Dominant alleles revert intragenically, e.g., *e665e2112*, recessive weak Unc (probable null phenotype). [Brenner 1974; Park and Horvitz 1986a] [JT]

unc-59 I 22.49 e261 : poor backward movement, forward better; thin; vulva variably abnormal, often protrusive, sometimes ruptured; many postembryonic lineage abnormalities resulting from variable failures in cytokinesis; gonad lineages sometimes defective; variable defects in neuroanatomy; males have very abnormal tail anatomy. ES2 ME0. OA3: *e1005* (pka *unc-88*), *e1465, n391*. [Brenner 1974; White et al. 1982] [MT]

unc-60 V –18.92 e723 : limp paralyzed or very slow; thin; Egl; abnormal muscle ultrastructure with large aggregates of thin filaments; recessively suppressed by *sup-12*. ES3 ME0. OA>10: *e677* (pka *unc-66*), *e890* (both resemble *e723*), *e890, s1310* (induced on *eT1*), *s1586* (500-bp deletion, larval-lethal). Also *r398, s1307* (both antidystrophic alleles).

CLONED: 1.3- and 0.7-kb alternative transcripts encoding 165-aa and 152-aa predicted proteins with 38% identity, sharing only first exon and first methionine; both have similarity to actin depolymerizing proteins (cofilin, destrin).

[Waterston et al. 1980; McKim et al. 1994] [BC]

unc-61 V 6.49 e228 : poor backing, irregular waveform in forward movement; thin; protrusive vulva; variable defects in neuroanatomy; male tail very abnormal (rays absent, spicules reduced, etc.). ES3 ME0 NA1. [Brenner 1974; Siddiqui and Culotti 1991] [SQ]

unc-62 V –5.49 e644 : slightly slow, irregular, sometimes rippling movement, especially in reverse; slightly dumpy; variable abnormalities in VD and DD commissures; male tail abnormal, bursa small, fan reduced, rays variably absent; 19% of embryos Nob. ES2 ME0. OA2: *s472*spo (pka *let-328*, lethal, probable null), *ct344* (pka *nob-5*, partial maternal-effect Nob, disorganized posterior). [Brenner 1974; Johnsen and Baillie 1991] [BC, BW]

unc-63 I –0.24 e214 : weak kinker, slow, inactive; resistant to 1 mM levamisole, sensitive to hypo-osmotic shock; elevated acetylcholine levels. ES3 ME2. OA>50: *x13* (pka *lev-7*, Lev, Ric, poor backing; ES3 ME3), *x18, x37*, etc.

EXHIBIT B

1: Neuron. 1997 Jan;18(1):107-19.

unc-8, a DEG/ENaC family member, encodes a subunit of a candidate mechanically gated channel that modulates C. elegans locomotion.

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Mechanically gated ion channels are important modulators of coordinated movement, yet little is known of their molecular properties. We report that C elegans unc-8, originally identified by gain-of-function mutations that induce neuronal swelling and severe uncoordination, encodes a DEG/ENaC family member homologous to subunits of a candidate mechanically gated ion channel. unc-8 is expressed in several sensory neurons, interneurons, and motor neurons. unc-8 null mutants exhibit previously unrecognized but striking defects in the amplitude and wavelength of sinusoidal tracks inscribe as they move through an E. coli lawn. We hypothesize that UNC-8 channels could modulate coordinated movement in response to body stretch. del-1, a second DEG/ENaC family member coexpressed with unc-8 in a subset of motor neurons, might also participate in a channel that contributes to nematode proprioception.

PMID: 9010209 [PubMed - indexed for MEDLINE]